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LAWRENCE LIVERMORE RESEARCH ADVANCE MAY IMPROVE THE WAY CANCER IS DIAGNOSED AND TREATED

WASHINGTON, D.C. -- Scientists from Lawrence Livermore National Laboratory today announced the transfer of an innovative technology that has the potential to dramatically improve the diagnosis and treatment of many cancers.

Known as chromosome painting, the technique uses specially-developed fluorescent dyes to stain or "light up" chromosomes for much more rapid and accurate detection of chromosome abnormalities.

In one of LLNL's most important technology transfers to date, the development is being brought to the market this month as a research product called Whole Chromosome Paints by Imagenetics, an Illinois-based medical diagnostics company.

The announcement was made today as scientists gathered here for the eighth International Congress of Human Genetics.

The key discovery made by LLNL biomedical scientists is that deoxyribonucleic acid (DNA), the blueprint of living matter, and chemicals can be used to stain or "light up" entire chromosomes within cells.

The advance was produced by a team of researchers led by biomedical scientists Dr. Joe Gray and Dr. Dan Pinkel. Other team members include: Collin Collins, Rick Segraves and Wen Lin Kuo.

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Attachment 1

Under Imagenetics' research and development program, a novel technology was invented that allows different-colored fluorescent markers to be directly attached to DNA. This greatly simplifies the chromosome staining procedure and makes it easily usable by most researchers. The advance also permits simultaneous analysis of at least five different chromosomes.

Imagenetics also developed manufacturing processes that have dramatically reduced the cost of the reagents.

Researchers hope improved diagnoses of chromosome abnormalities will eventually permit the development of individualized and improved cancer therapies based on these abnormalities instead of general treatments now in use.

Currently, fewer than 10 percent of the 1.2 million annual cancer cases in the United States are diagnosed -- and treated -- on the basis of chromosome abnormalities.

Along with its expected value in cancer research and diagnoses, the technology is now playing a vital role in LLNL studies about the effects on people from radiation and chemical exposures.

Research Advance Will Help Understand Cancer

"This technology is an important advance and will enable researchers to better understand the genetic basis of cancer," said Dr. Al Deisseroth of the University of Texas M.D. Anderson Cancer Center in Houston.

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"With the ability to identify the genetic changes in evolving cancer and leukemia cells, along with the relationship of these changes to cell behavior, for the first time we will be able to identify and then direct therapy to specific targets," Deisseroth explained.

Researchers at other major medical institutions believe the LLNL developed technology will make diagnoses of leukemia "much easier" and assist in better understanding the genetic basis of solid cancer tumors.

Research funding that led to the development of the Whole Chromosome Paints technology was originally provided by the U.S. Department of Energy and the National Institutes of Health, and then by Imagenetics through a research contract with LLNL.

Under a 1989 funding and licensing agreement -- a collaborative industrial research program with the University of California Regents -- the Whole Chromosome Paints will become a product line of Imagenetics, which is based in Naperville, Ill. LLNL is managed by the University of California.

The Whole Chromosome Paints will be sold to research laboratories worldwide by Gaithersburg, Md.-based Life Technologies, Inc., a supplier of biological products for life science research. They will be available through the GIBCO BRL brand as WCP™ DNA Probes.

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Nine of the paints for the 24 human chromosomes will be sold beginning later this month, Imagenetics' Tom Mozer said, adding the remaining 15 paints will be available within six to 12 months.

Basic Research Pays Dividend

"Over time, thousands of people will benefit from this development through improved cancer and leukemia diagnoses," said Dr. William Davis, associate director of the University of California Office of Technology Transfer. "This effort is a textbook example of cooperation between a national lab, university and private industry."

Imagenetics' Mozer called the Whole Chromosome Paints an "outstanding example of how basic research funded by the U.S. government leads to new technologies.

"When these technologies are transferred to U.S. industry for development into products, they can be used to improve human health and to enhance our nation's economic competitiveness," Mozer added.

Along with these advantages, co-inventor Joe Gray noted that the technology transfer to a commercial firm like Imagenetics also ensures there will be high-quality, reliable paint probes for research and other biological applications.

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The new technology allows researchers to intensely and specifically stain selected chromosomes or subregions according to their DNA sequence.

In this approach, DNA in the cells or chromosomes is heated so that the DNA, which is normally a double helix of complementary strands, melts and the strands separate.

The DNA to be studied is then incubated with chemically modified and denatured nucleic-acid probe sequences that are complementary to DNA sequences in the chromosomes to be stained.

The incubation conditions are such that the probe binds only to the target DNA sequences that are complementary. In the past, the bound probe was made visible by treatment with a fluorescent reagent that was able to bind with high affinity to the probe's chemical modification. With the Imagenetics advance, this step is eliminated because the fluorescent markers are directly attached to the DNA probes.

The key to the chromosome staining approach is in obtaining the chromosome specific paint or probe.

Chromosome specific staining is achieved by inhibiting the nonspecific, repeated sequences from a special recombinant DNA library. Under the agreement, Imagenetics has access to LLNL's special libraries of recombinant DNA from which to synthesize their special chemical paints.

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A major advantage of the technique is that it permits intense staining of selected chromosomes in non-dividing cells. The need for expensive and time-consuming cell-culture methods is thereby eliminated.

Because chromosomes are tightly localized in the nuclei of non-dividing cells, targeted regions are visible as bright spots within the nucleus.

Imagenetics is funding teams of clinicians at leading medical institutions to join their researchers to move this technology into routine use in medicine.

In addition to the M.D. Anderson Cancer Center, the Whole Chromosome Paints have undergone their main research testing for a year or more at three other institutions, the Mayo Clinic, the University of Michigan Medical Center and the University of Chicago.

Dr. Robert Jenkins, co-director of the Mayo Clinic's Cytogenetics Laboratory, anticipates the Whole Chromosome Paints will make diagnoses of leukemia "much easier."

"This technology may well be used routinely within a few years and we could end up staining every bone marrow specimen we examine in the Mayo Clinic in this way," Jenkins stated.

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Paints May Be "Gold Standard"

Jenkins added that the new technology may well become the "gold standard" in identifying several types of leukemia and other genetic abnormalities.

At the University of Michigan Medical Center, Dr. Jeffrey Trent has employed the Whole Chromosome Paints to study chromosome changes in common adult cancers like breast cancer and melanoma.

"Solid cancer tumors are extremely complex genetically and these paints may well help define the genetic alterations that are important in these disorders," Trent said.

Imagenetics' Mozer noted, "We are extremely encouraged by the research testing, especially on the chromosome eight paints, for the genetic evaluation of cancer cells.

"The Whole Chromosome Paints allow the color-coded identification of chromosomes associated with many types of cancers," Mozer said. "In effect, we have lit up the cell's chromosomes, so that we can much more easily recognize the chromosome abnormalities that are associated with cancer."

It is anticipated that more specific reagents than the Whole Chromosome Paints will be prepared and that these reagents will be submitted to the U.S. Food and Drug Administration for consideration as clinical diagnostic products, Mozer said.

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To further their research and explore its medical value, paint probe inventors Joe Gray, Dan Pinkel and their team moved in July from LLNL to the University of California, San Francisco.

LLNL Approach Helps Breakthrough

Gray, now the director of UC San Francisco's Molecular Cytometry Division within the Department of Laboratory Medicine, credits LLNL's multi-disciplinary approach to science and engineering as one of the key factors behind the Whole Chromosome Paints breakthrough.

In particular, Gray cites as important the combination of the disciplines of engineering, biophysics, mathematics, molecular biology and cell biology.

END MAIN NEWS RELEASE

Additional background information is hereby provided.

During research and experiments over the past two years, the Whole Chromosome Paints technology has proven to be more accurate and rapid than existing diagnostic technologies, researchers believe.

Because of their speed, the paints will eventually permit much more rapid analysis of the effectiveness of cancer treatments and, as a result, the chance to change treatments in the view of M.D. Anderson's Dr. Al Deisseroth.

"Current analytical techniques are too work intensive and the use of patient survival as a measuring point of therapy takes too long," Deisseroth said. "The Whole Chromosome Paints can help develop much more efficient ways to analyze the results of therapy."

At the Mayo Clinic, Dr. Robert Jenkins and Dr. Gordon Dewald have employed the paints to count chromosomes and have found the probes "vastly increase" their ability to detect chromosome abnormalities.

Paints Light Up Chromosomes

The Whole Chromosome Paints are helpful, Jenkins said, because they use fluorescent dyes to light up chromosomes, allowing better analysis during a brief time known as metaphase, when chromosomes are easily visible under a microscope.

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While current leukemia detection techniques permit only about 10 percent of metaphase cells from bone marrow specimens to be analyzed, the paints allow "nearly every metaphase" cell to be studied, Jenkins said.

Thus, researchers who can now locate only 20 usable metaphases in about four hours, may be able to detect about 100 within 30 minutes with the paints, allowing more accurate analyses, according to Jenkins.

Another way Jenkins has applied the probes is to identify chromosome translocations, which occur when part of one chromosome is exchanged with a different chromosome. For example, in chronic myelogenous leukemia, part of chromosome nine is exchanged with a portion of chromosome 22.

"Sometimes, analysis is made more difficult because parts of one chromosome will look like a natural part of another chromosome, " Jenkins said. "But with the paints, the fluorescent dyes light up the different chromosomes in two distinct colors, showing the translocation."

A key to the LLNL-developed technology is that certain DNA will only bind or attach itself to the same chromosome from which it originated, no matter which human's blood or tissue specimens are tested or used.

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With the paints, researchers can thus more easily spot chromosome abnormalities, such as an extra chromosome or chromosome translocations, that are often indicative of cancer and leukemia.

Current techniques require researchers to engage in time-consuming and often difficult microscopic examination of cell samples for visual evidence of chromosome abnormalities.

Another reason why more cancer cases are not diagnosed genetically, according to Imagenetics' Mozer, is that there is a shortage in the U.S. of cytogeneticists, the researchers who perform the chromosome analysis.

"With new advances, we believe the era of individualizing cancer treatments is just beginning," said Whole Chromosome Paints co-inventor Joe Gray. "Our research is going in the direction of understanding the evolutionary progression of tumors and hopefully identifying features that will permit therapy to be individualized."

In addition to being utilized for cancer studies, the Whole Chromosome Paints have been useful in research for detecting human chromosome abnormalities caused by environmental accidents.

Scientists at LLNL are utilizing the paints to study the effects of radiation exposure on people from different accidents, such as the Chernobyl nuclear power plant release.

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The paints are especially valuable in identifying chromosome translocations. This particular abnormality is difficult to detect by other methods. Because translocations have long lives, their measurement allows researchers to estimate cumulative lifetime exposures in people from radiation and chemicals.

More Targeted Probes Due

The Gray-Pinkel team is now developing more specific and targeted research diagnostic tools than the Whole Chromosome Paints, ones that will identify diseases based on gene abnormalities in specific areas of chromosomes.

In one study of their more targeted approach, scientists at LLNL, Stanford University Medical Center, the University of Chicago Medical Center and Memorial Sloan-Kettering Cancer Center compared that technology with two traditional diagnostic techniques for leukemia.

The researchers examined 11 samples -- seven from patients with chronic myelogenous leukemia and four from normal cell samples. While the newest DNA probes identified all 11 samples correctly, errors were found with both of the standard techniques.

The newest DNA probes are also faster than most standard techniques, allowing analysis within 24 hours, while most of the other diagnostic procedures require several days to weeks because of the need to grow cells in culture or find chromosomes at particular points in cell division.

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For the future, Gray believes the use of high-resolution microscopes, ultra-sensitive detection cameras and image analysis software will facilitate, and possibly allow, the automation of detecting genetic abnormalities.

"The current reality of our technology is that you can spot one cancer cell among 1,000 normal cells," Gray said. "The promise of the technology is that we may one day be able to find one cancer cell among 100,000 normal cells, most likely with the moré targeted location specific probes."

Imagenetics is a medical diagnostics firm specializing in genetic and cancer diagnostic systems, providing both instruments and reagents for research and clinical applications.

Life Technologies, Inc., develops, manufactures and supplies more than 2,000 GIBCO BRL brand products used principally in life science research and the commercial manufacture of genetically engineered products. A publicly held company, the firm believes it is a leading supplier of sera, other cell growth media, as well as enzymes and other biological products necessary for recombinant DNA procedures.

Lawrence Livermore National Laboratory, which is managed by the University of California for the U.S. Department of Energy, conducts research and development important to a variety of national goals, including national defense. Current research programs include

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weapons, energy, biomedicine and the environment. The Laboratory also has a longstanding commitment to developing new methods and technologies to protect the environment and to enhance the nation's economic competitiveness.

OTHER RESOURCES ARE AVAILABLE UPON REQUEST. THEY ARE: PHOTOS OF WHOLE CHROMOSOME PAINTS CO-INVENTORS JOE GRAY AND DAN PINKEL, AS WELL AS THREE ADDITIONAL NEWS RELEASES DESCRIBING IN GREATER DEPTH THE RESEARCH AT THE M.D. ANDERSON CANCER CENTER, THE MAYO CLINIC AND THE UNIVERSITY OF MICHIGAN MEDICAL CENTER.

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